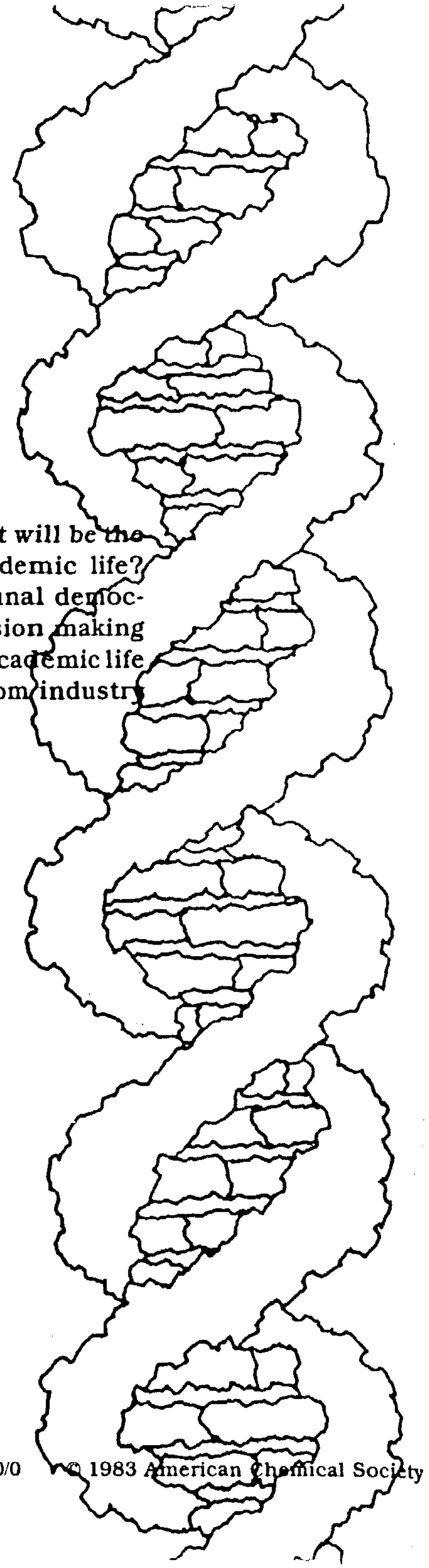

Who makes the decisions and what will be the effects on public health and academic life? Some kind of local *ad hoc* communal democracy may be one approach to decision making and keeping the public informed. Academic life may undergo changes resulting from industry involvement.

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Ethical and Institutional Aspects of Recombinant DNA Technology

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I believe I qualify to speak on the subject of this report on at least two distinct historical grounds. The first is that, by an accident of scientific history, I happened to be the one who, with my associate Mary Human, discovered the first instance of restriction and modification of DNA, the basis for recombinant DNA technology. This was in 1951, and the discovery was not done by working directly on DNA. What we found was that a certain bacteriophage could or could not multiply in a certain bacterial host depending on which host it had previously infected.

This discovery was immediately generalized to other systems. It was soon clear that restriction

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had to do with a specific breakage of DNA when it entered the wrong bacterium. But it took several years, a decade in fact, before anyone could isolate the restriction enzymes. These proved to be a special class of enzymes that would cut DNA specifically at certain precise sequences in their nucleotide language unless certain bases were methylated. These enzymes, therefore, could be used to generate DNA fragments that could then be joined to others as desired—the basis of recombinant DNA technology. This technology resembles, at least formally, the technology of electrical circuits, with promoters, operators, terminators, and attenuators taking the place of batteries, resistors, capacitors, transformers, and so on. As I shall point out later, despite a genetic terminology that may be alien to some, the recombinant DNA circuitry is basically as simple as electrical circuitry. A good electrician is just as easy or as hard to come by as a good DNA recombinationist.

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If my first historical claim in this area is to have been an early warrior, my second claim is to have been an early worrier. In the 1960s, long before Asilomar, and guidelines for research, and P1–P4 classification or any recombinant DNA experiments I was concerned with genetic engineering of the nuclear transplant type. I worried that the new potentialities of cell biology and genetics would raise a number of issues such that the public and the scientists would not see eye to eye. I wrote a few articles on this subject, some of which received alarmist titles from magazine editors. I suggested at that time that agencies such as the National Academy of Sciences and possibly the United Nations might do well to set up committees or task forces to advise scientists and keep the public informed of the possible applications and consequences of genetic engineering. Reassurance, I believed, would make it possible to minimize conflicts, while responsible leadership would help prevent foolish or dangerous applications.

Be that as it may, by the late 1960s the actuality of a technology based on splitting, rejoining, and transferring segments of DNA was recognized. Within a decade such technology has become not only a reality but an industry—for the time being, at least, a corporate rather than a production concern. In its growth, recombinant DNA technology had to go through an adolescent crisis, in which Asilomar might be compared to an awareness of sex, the National Institutes of Health (NIH) guidelines to an attempt at parental tutelage, and the current scene to the assumption of adult responsibility.

In today's discussion I would like to touch upon three aspects of the recombinant DNA story both past and present. These are, first, the question of public health dangers; second, the problem of decision making; and finally, the ethical impact of recombinant DNA technology on institutional life.

Potential Public Health Dangers

The question of public health dangers was bound to arise with the public, in the press, and among scientists, as the awareness of DNA experimentation increased. It was thrown into sudden relief by the Asilomar conference of 1976. Press reporters, always eager to sensationalize, were at hand to feed on what for many people (I was not there) was a serious discussion of how to proceed; for some others, it was an ego trip, or rather a super-ego trip. The idea that they were dealing with potential dynamite made some scientists feel grand; the sense that they were dealing with it as responsible citizens made them feel deliciously humble if not heroic. But, as often happens in our media-infected society, the show threatened to overshadow the reality. The absolution that some scientists were hunting for, like Lewis Carroll's snark threatened to overwhelm the hunters. The snark threatened to be a bojum.

From the very beginning it was my belief as a microbiologist and a geneticist that shifting bits of DNA from cells to plasmid and to bacteria, fashioning chimeric genomes and letting them loose into our urban sewers would involve no danger beyond what human incompetence is always apt to generate. Clearly, placing genes for botulinus toxin or for plague into *Escherichia coli* would be irresponsible, as irresponsible as it would be to handle *Clostridium botulinum* or *Pasteurella pestis* incompetently in the laboratory. But I never could buy the nebulous argument that creating "a new organism that did not yet exist in nature" was intrinsically dangerous. Each time a human being is born it is a new organism, a new genome, which may turn out to be a Newton, or an Einstein, or an Attila, or a Hitler.

The discussion of dangers, as you certainly remember, was particularly bitter in Cambridge, Mass., where at times it verged on the preposterous. The City Council, having on its hands both Harvard and the Massachusetts Institute of Technology, held public hearings, where people stood up and compared recombinant DNA technology to nuclear plants and nuclear bombs. The vision of cockroaches spreading out from a Harvard laboratory to infest the city of Cambridge with recombinant monsters was raised by distinguished scientists in words fit for science fiction.

Behind the surface layer of worry there was a hidden agenda, which deserves serious analysis and to which I shall return. But the enormity of the horrors vividly evoked made it hard to discuss soberly the other issues, at least in Cambridge. Personally, I tried in a few letters to newspapers to separate the various issues, but without much success. I was blamed by fear-mongers as well as by pro-recombinant DNA colleagues, a clear indication that the problem had moved from the technical to the political arena.

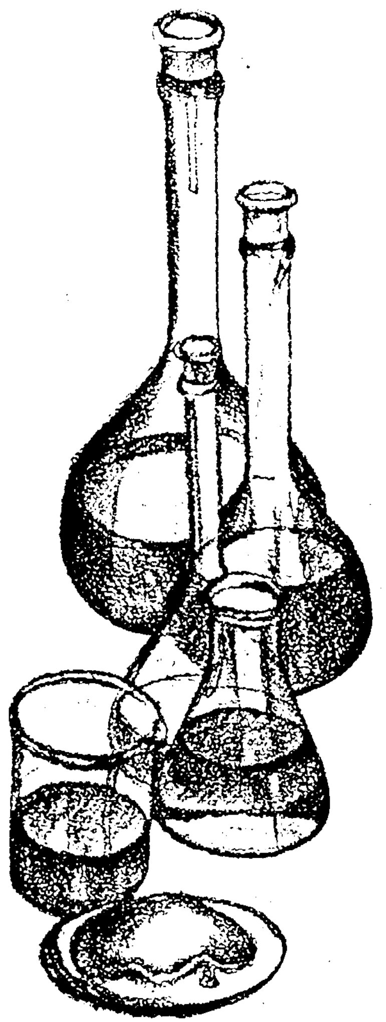
For better or for worse, the sense of danger is something that tends to decrease the longer one lives with the supposed danger. This may be unfortunate in the case of real dangers like atom bombs, but it worked out well for recombinant DNA.

Problem of Decision Making

This is a political problem that involves questions of power and is, therefore, not soluble except possibly in the much broader framework of who does or who should wield power. But examination within the microcosm of recombinant DNA technology may be instructive.

The protagonists in the confrontations of 1976–77 were not divided by opposite sets of values; rather, values conflicted with goals. The scientists wanted to go ahead with their work with a minimum of regulation and a maximum of protection. They were prepared to abide by the guidelines (although most of them believed them to be unnecessary), because the guidelines represented official absolution. In fact, it is remarkable how much the guidelines were actually observed; as remarkable as I always find it that people refrain from smoking in the non-smoker section of airplanes. People don't want trouble if they are allowed to do their work.

But scientists by-and-large failed to understand, or at least to come to grips with, the real issue posed by their critics: the issue of who makes the decisions. When the decision concerns which research should be funded and to what extent the public, at least in nonrevolutionary periods, is willing to leave the decision to



Congress and to peer reviews. Even in the days of revolt in the 1960s, the question of decision making in relation to funding and performing of basic research was raised only in a perfunctory way. But the situation is different when one goes from science to technology, for example, to recombinant DNA technology. Interestingly enough, a populace that is willing to trust to its elected representatives the right to manufacture, and maybe use, thousands of hydrogen bombs can be roused by the idea that scientists may generate noxious microbes. Proximity helps propagate the concern: Harvard and MIT in Cambridge are not only educational institutions; they are employers, and landlords, and taxpayers (or nonpayers, whatever the case may be). Politics becomes a complex concern, but at its core is the unresolved dilemma: in a society permeated by technology, who decides what is to be done and what not? Is von Neumann's famous statement valid, that in the area of technology "what *can* be done *will* be done?"

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I do not claim to have an answer. I tried to deal with some of the general questions in this area in a lecture entitled "Slippery When Wet" delivered at the American Philosophical Society in 1971. As evidence of the controversiality of this subject I may mention that months later I received a note from my friend Philip Handler, saying: "I am sorry I did not hear your talk. I read your lecture and I want you to know that I completely disagree."

Given that there is no generally satisfactory answer, let me try to explore the subject pragmatically for the recombinant DNA case. In Cambridge what was done was for the City Council to appoint a committee, ranging from doctors to nurses to housewives to laborers. The committee invited testimony and visited laboratories. It did what best can be done: to learn the facts and issues and to explain them to others in their report. It recommended that the city go along with the NIH guidelines but that it retain the power of ordinance control in order to reassure the public that their interests were protected locally as well as in Washington. It allowed cooling off of tempers without stifling debate. It was a good, if not perfect, exercise in democracy.

But the problem remains: who does the deciding? Essentially, it is a problem of imperfect democracy. Our elected officers cannot be depended upon to have infinite wisdom or freedom from pressures. Power in our democracy is dual: government power and corporate power, the relation between the two being generally asymmetrical. How is the public to know whether a government decision aims at the well-being of the public or is a response to corporate pressure? I personally feel that a certain distrust in the path of technology development and application is justified and desirable, not just because of physical dangers but because of possible dislocations of the power structure. I was, fortunately, enough of an expert in the field of recombinant DNA to realize the minimal level of danger. But what do I know about miniaturization of electronic circuits, or about child psychology, to be sure that TV or video games will not hurt society as I know it and like it?

The example of Cambridge, however imperfect, suggests one possible way for the public to act: a sort of local *ad hoc* communal democracy added to the electoral one in which our confidence has unfortunately been shaken. As far as scientists are concerned, it may well be that some sensible kind of machinery may be established for debating the pros and cons of emerging technologies. This may provide a forum through which to communicate with the public, its elected representatives, as well as other corporate interests in a sounder way than through the shrill voice of commercial media.

The press has contributed in recent months to bring to the fore the question of the role of scientists in the industrial application of recombinant DNA technology, which is the third and last problem I wish to discuss. For once in the history of technology, scientists have in the field of DNA technology become aware of the potential fruits of their work before or at least at the same time as corporate interests. And these fruits can be the sweet ones of medical progress—the gift of Asclepius—as well as the equally sweet ones of monetary gain—the reward of Danae. Faced with the possibility of a few geneticists and biochemists becoming millionaires and many others being able to supplement their salaries by serving as industrial consultants, some sections of the press and the public, and some old fashioned university administrators, have raised the specter of corruption.

I confess that I have little sympathy for this targeted defense of academic purity. In the first place, making money out of private companies established specifically for that purpose has been the traditional way among university engineers and I believe also university chemists. In my own institution, for example, a professor may be on the board of one or several corporations, may actually found such a corporation, may consult for one or more, the requirement being that he or she not receive a regular salary and be paid only in stocks, options, and consultant fees. Conflicts of interest with the university are of course to be avoided.

Even apart from the precedents for industrial involvement on the part of university professors, I find it ludicrous that in a society like ours, where the profit motive is not only recognized but celebrated everywhere from the cradle to the Presidency—where several presidents of the United States have taken advantage of questionable loopholes in the tax laws in order to enrich themselves; in which the public watches without batting an eye while the FBI illegally entraps with bribes a number of readily bribable legislators—I find it ludicrous, I repeat, that so much fuss be made at the chance that a few scientists may become guided by profit rather than by the purest dream of discovery. Why should molecular biologists be purer or more virginal than chemists or engineers? We are none of us angels or spartans. But I am willing to bet that among all reasonable-sized fortunes that will be made in the next 20 years, those made by university scientists will be ethically at least as clean as those of lawyers, bankers, or members of Congress.

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Yet, the question of university research in the area of DNA technology has some more complex aspects. One aspect, which has already been debated in faculty meetings as well as in newspaper columns, is that of corporate involvement of the universities themselves in biological research. When a university owns a spaghetti factory or a car rental business, it simply takes its corporate risks like any investor. The only special problem universities have to consider is their relations to the Internal Revenue Service. Ethical considerations apply equally to universities and to other businesses.

Trouble may come, however, if corporate research sponsored by a university is done within the university itself, by individuals who are also paid to teach and to do basic research sponsored by outside agencies. Such an arrangement is quite dangerous. The scientists working on corporate research acquire a special position because they generate industrial profit in addition to or instead of the nonprofit value of teaching and pure research. They will be perceived by their colleagues as being a special and privileged group, part of the industrial rump of the university rather than of its educational front. This kind of trouble is bound to arise not only when a university goes into business for itself (something that Harvard half-heartedly decided not to do) but also when a university accepts to do targeted research specified by a corporate donor. This inevitably results in a dual system of research appointments. It might be preferable if scientists who work on such targeted contracts, as contrasted with broadly exploratory ones, were physically or academically segregated from the regular faculty, preserving the purity of the tax-exempt ghetto.

In any case, it is important to avoid having within a university department two classes of faculty scientists, those who hold purely academic jobs and those whose applied work brings a financial reward to the institution. Such a dichotomy will inevitably give rise to internal suspicions and lead to faculty demoralization. Recall the situation described, of all places, in the second chapter of Genesis: two fellows named Abel and Cain got into trouble when the big boss started making distinctions between the value of their respective outputs. As you will recall, the resulting strife led to the first major unpleasantness in creation science.

There is a scientific aspect of recombinant DNA research that is not yet generally realized and may soon affect some of the financial and industrial characteristics of this field. Until a couple of years ago, recombinant DNA research was the cutting edge of biological science. A few great experts and pioneers stood out in the same way as the great physicists of the 1920s and '30s stood out. Those were the undisputed leaders whom governments called upon in times of crisis to produce strategic bombing patterns or atom bombs.

What is happening today in DNA technology, however, is very different. The technology that may have industrial uses has proved to be so simple and unsophisticated that any properly trained undergraduate can in a few months become an expert, or at least a proficient practitioner. At the moment there appears to be little to be discovered except possibly some refinements of technique. The astuteness is almost purely commercial: to decide which gene product will sell and then go about the series of steps needed to single out the corresponding gene and put it to work. The chance of success in any one case may be reasonably greater than zero.

What I mean is that, with few exceptions, the great experts are not specially likely to become unique leaders in the industrial application of DNA research. I might do better buying stock in a large established pharmaceutical firm just entering this field than in one of the glamour companies led by my fellow scientists. Success may depend more on the wisdom of knowing what products to go after than on the refinements of scientific technology.

What this implies is that, while substantial input of industrial capital may help accelerate the application of DNA technology to practical uses, it is not needed for the advancement of molecular biology. Unless I am grossly mistaken, major advances in understanding the organization and functioning of DNA will still be made in universities. They will be made by scientists who pursue their work with little concern for applications. They may well be stimulated by what they learn while acting as industrial consultants, but they will not gain very much if while working in the lab they worry about stock options. This has been the story in chemistry: the close, intimate relation between university chemists and the chemical industry has stimulated great advances, which, however, have come mostly from the campus rather than from the factory. Wealth, or the mirage of wealth, does not hurt scientists any more than it does poets or musicians or businesspersons. But great symphonies or poems have seldom been composed just to make money. It would be unfortunate if some of the best minds in biology were distracted by financial preoccupation from pursuing their most valuable activity.

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